Published in final edited form as:
Circulation. 2011 August 2; 124(5): 642–650. doi:10.1161/CIRCULATIONAHA.111.021774.

Modulation of Anthracycline-Induced Cardiotoxicity by Aerobic Exercise in Breast Cancer: Current Evidence and Underlying Mechanisms

Jessica M. Scott, PhD[1], **Aarif Khakoo, MD**[2], **John R. Mackey, MD**[3], **Mark J. Haykowsky, PhD**[3], **Pamela S. Douglas, MD**[4], and **Lee W. Jones, PhD**[4]

[1]NASA Johnson Space Center, Universities Space Research Association, Houston, Texas, USA

[2]University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

[3]University of Alberta, Edmonton, Alberta, Canada

[4]Duke University Medical Center, Durham, North Carolina, USA

Introduction

Anthracycline-containing chemotherapy (e.g., doxorubicin, DOX), is well known to cause dose-dependent, progressive cardiac damage clinically manifest as decreased left ventricular ejection fraction (LVEF) and, ultimately, heart failure (HF) (Table 1).[1, 2] Unfortunately, the only clinically accepted method to minimize injury is dose modification and/or therapy discontinuation.[3] An important current challenge in breast cancer management is therefore to maximize the benefits of DOX, while minimizing cardiac damage. Identification and examination of new interventions to prevent and/or treat DOX-induced cardiotoxicity are urgently required.

Aerobic exercise is one non-pharmacological therapy that promises to attenuate DOX-induced cardiotoxicity. Aerobic exercise is well documented to improve systolic and diastolic function and attenuate pathologic cardiac remodeling, resulting in improved exercise tolerance and resistance to fatigue during exertion in patients with HF.[4, 5] The cardioprotective properties of aerobic exercise in the context of DOX have, in contrast, received scant attention. It is not generally used in cancer patients despite its lack of ‘side effects’ and the paucity of alternative strategies to prevent/treat DOX associated cardiac damage.

As a first step in the possible use of exercise in cancer patients, we reviewed the mechanisms of DOX-induced cardiotoxicity and the available evidence supporting the utility of aerobic exercise to prevent/treat cardiac injury. We also explored the molecular mechanisms that may underlie the cardioprotective properties of aerobic exercise. These findings have implications for future research regarding the application and effectiveness of exercise and DOX treatment in humans.

Correspondence: Jessica Scott, PhD, Exercise Physiology and Countermeasures, NASA Johnson Space Center, Universities Space Research Association, 2101 NASA Parkway, Houston, TX 77058. Phone: 281-483-8398. Fax: 281-483-4181. jessica.m.scott@nasa.gov.

Disclosures: The authors declare no conflicts of interest.

Mechanisms of Anthracycline Cardiotoxicity

The mechanisms underlying the antitumor function of anthracyclines have been described previously.[6–8] Among the proposed mechanisms of cardiac injury, DOX-induced generation of reactive oxygen species (ROS)[9, 10] is a central mediator of numerous direct and indirect cardiac adverse consequences (for review see Minotti et al.).[11] Here we will briefly review DOX-induced oxidative injury relevant to aerobic exercise and relating to: 1) accelerated myofilament apoptosis,[12] 2) suppression of myofilament protein synthesis,[13] 3) alterations in cardiac energy metabolism,[14] and 4) ultrastructural changes to myocytes[15] (Figure 1).

Myofilament Apoptosis

Myocyte cell death stems from the DOX-induced generation of ROS, which, in turn, activate a multiplicity of signaling pathways that determine cell fate. A key pathway involves activation of the tumor suppressor protein, p53.[16] p53-dependent apoptosis involves the transcriptional activation or inhibition of certain target gene pathways such as mitogen activated protein kinases (MAPK). Zhu et al.[17] found that 24h of DOX exposure induced apoptosis in cardiac myocytes through p38 MAPK dependent activation, whereas Yamamoto et al.[18] reported that p38-MAPK and c-Jun N-terminal kinases (JNKs), but not extracellular-signal-regulated kinases (ERKs), were activated by DOX in cardiomyocytes. Inhibitors of p53,[19] p38-MAPK and JNK[20] have all been shown to prevent DOX-induced apoptosis, suggesting that interventions targeting p53 or its downstream pathways could attenuate LV systolic dysfunction and decrease myocyte apoptosis.

Suppression of Myofilament Protein Synthesis

Suppression of sarcomere protein synthesis through depletion of cardiac progenitor cells (CPCs) or GATA-4 dependent gene expression is also postulated to contribute to DOX-induced cardiac injury.[21] De Angelis et al.[22] reported that DOX exposure significantly reduced the population of CPCs, raising the possibility that CPC death may represent a primary event responsible for impaired myocyte turnover, accumulation of senescent cells, and the onset of ventricular dysfunction. Interestingly, delivery of syngeneic CPCs into DOX-induced failing hearts caused regeneration of cardiomyocytes, leading to improved LV performance and overall survival.[22] DOX also downregulates GATA-4, a CPC regulatory transcription factor and an essential survival factor for postnatal cardiomyocytes.[23, 24] Decreased GATA-4 levels following DOX exposure may, in turn, inhibit sarcomere protein synthesis, thus contributing to LV dysfunction. Accordingly, restoring or preventing GATA-4 and/or CPC depletion could be exploited as a novel means to ablate DOX-induced cardiac toxicity.

Ultrastructural Changes to Myocytes

ROS also cause alterations in calcium homeostasis leading to systolic (contractile) and diastolic (lusitropic) dysfunction.[25] DOX stimulates calcium release and inhibits sarcoplasmic reticulum (SR) calcium reuptake, resulting in cytosolic calcium overload.[9, 26, 27] This calcium overload may contribute to impaired contractile function by: 1) promoting release of the proapoptotic factor cytochrome c,[28] and/or 2) activating the cysteine protease calpain.[29] Calpains initiate turnover of both regulatory and structural myofibrillar proteins through cleavage and release of large polypeptide fragments.[29, 30] To our knowledge, the role of calpain in DOX cardiac injury has not been investigated.

DOX also modulates structural proteins such as titin. Lim et al.[12] reported that short-term DOX exposure leads to significant degradation of titin in cultured adult rat cardiomyocytes. This degradation occurred in concert with impaired relaxation as measured by tau. Intriguingly, pretreatment of myocytes with calpain inhibitors for 1 h prior to DOX

preserved the ratio of titin to myosin heavy chain similar to control levels, and reduced the DOX-induced myofibrillar disarray.[12]

Alterations in Cardiac Energy Metabolism

The heart requires adenosine triphosphate (ATP) to sustain contraction and relaxation. As such, deficiencies in cellular homeostasis are important factors in the development of cardiomyopathy.[31–33] DOX reduces cardiac energy reserves by lowering ATP and phosphocreatine (PCr) levels as well as the PCr/ATP ratio.[34–36] In the normal heart, AMP-activated protein kinase (AMPK) plays a crucial role in protecting cardiac cells from perturbations in energy homeostasis via activation of catabolic pathways to generate ATP.[37] DOX reduces the level of both AMPK protein and its basic activation state, which leads to decreased phosphorylation of anti-acetyl-CoA carboxylase (ACC), an AMPK downstream target.[38] Lack of ACC inhibition results in impairment of fatty acid oxidation; thus, interventions that increase AMPK expression and/or normalize myocyte metabolism may be an effective strategy to offset cardiotoxicity. The mechanisms underlying inhibition of AMPK are not clear; alterations in gene expression and upstream signaling require further investigation. Other important factors activated in response to metabolic perturbations include hypoxia-inducible factor-1 (HIF-1) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 alpha). DOX has been shown to inhibit HIF-1 activity in human hematoma and prostate cancer cells,[39] therefore it appears biologically plausible that it may also modulate HIF-1 in the heart, although to our knowledge, no study to date has investigated this question.

Role of Aerobic Exercise in Modulation of Cardiac Function in Health and Disease

As summarized in Table 2, aerobic exercise training improves diastolic filling and increases stroke volume leading to augmentation of cardiac output and maximal oxygen uptake (VO_2max) in healthy women.[40–42] In addition to the wealth of evidence in healthy individuals, exercise has been the cornerstone of clinical rehabilitation in HF for over 15 years.[43] Aerobic exercise attenuates pathological LV remodeling, which is associated with LV dilatation.[44] The effects of endurance exercise in producing cardiac physiologic hypertrophy in murine and human models are well described.[45] The beneficial properties of endurance exercise are mediated, in part, through phosphoinostide 3-kinase (PI3k) / serine-threonine protein kinase (Akt) signaling axis via growth factors such as insulin-like growth factor-1 (IGF-1) and insulin,[46] although recent work demonstrated that reduction of the transcription factor C/EBPβ also plays a critical role.[47] These improvements have been shown to directly translate to increases in VO_2max, overall quality of life, and prognosis in individuals with HF.[43, 48] It should be noted, however, that the largest HF exercise trial to date found a non-significant reduction in re-hospitalization or death in patients randomized to aerobic exercise training, although such findings may, in part, be explained by an insufficient exercise training stimulus required to significantly modulate clinical outcomes.[49] Indeed, the median duration of exercise training in the intervention group was only 95 mins.wk^{-1}. A recent meta-analysis reported that exercise training is associated with significant improvements in EF among patients with HF,[50] suggesting that exercise can induce significant benefits for patients with cardiomyopathy. Higher volume (increased duration and/or intensity) exercise training interventions are likely required to significantly modulate clinical outcomes such as re-hospitalization or death.

Despite exercise-based rehabilitation being an integral component of clinical cardiac disease management, the molecular mechanisms underlying the effects of exercise remain incompletely understood. At the level of the cardiomyocyte, aerobic exercise improves the

maximal amplitude of shortening in unloaded cells[51–54] and increases the steepness of the sarcomere tension-length relationship, suggesting that the Frank-Starling mechanism is improved at the level of the single cardiomyocyte.[55] Thus, improved contractile capacity of the cardiac myocyte forms a cellular basis for improved systolic function and diastolic filling.

Role of Aerobic Exercise in Prevention/Treatment of DOX-Induced Cardiotoxicity

The strong cardioprotective properties of exercise in cardiac disease states create a compelling rationale to investigate the effects of aerobic exercise in the context of the DOX – cardiotoxicity relationship. To this end, we conducted a comprehensive review that identified 16 studies examining the efficacy of aerobic exercise to prevent (prior to and during therapy) and/or treat (following therapy) DOX-induced cardiotoxicity (Table 3). The data were obtained by searching PubMed using the following MeSH terms and text words: breast cancer, neoplasms, malignancies, cardiotoxicity, ejection fraction, exercise, exercise therapy, and exercise training. Relevant reference lists were also manually-searched. The major findings of these studies are briefly described in the following sections.

Exercise and Prevention of DOX-Induced Cardiotoxicity

Ten studies investigated the protective effects of aerobic exercise training prior to DOX administration. Overall, findings indicate that exercise prevents DOX-induced impairments in LV systolic and diastolic function. For example, Chicco et al.[62] found that dP/dtmax, a measure of LV systolic contractility, was 39% higher in the hearts of aerobically trained rats compared to sedentary controls; LV relaxation (dP/dtmin) rates also were 46% quicker in endurance trained animals. Four studies examined the effects of aerobic exercise *during* concurrent DOX therapy. Kanter and colleagues[69] demonstrated that swim training in mice decreased the histopathologic myocyte damage induced by DOX, while Hydock et al.[64] reported that aerobic exercise training protected against changes in HR, dP/dtmax, and dP/dtmin. Finally, our group recently found that aerobic exercise (treadmill running) in mice attenuated LV dysfunction following DOX exposure as well as ablated a DOX-induced increase in atrial naturietic peptide (ANP) and cardiac sarcoplasmic reticulum calcium transporter (SERCA2a). We also explored whether these findings extended to women with newly diagnosed histologically confirmed operable breast cancer receiving doxorubicin – cyclophosphamide (AC) neoadjuvant chemotherapy. In a phase II randomized design, patients were randomized to (1) AC alone, or (2) AC in combination with supervised endurance exercise training (cycle ergometry, $3x.wk^{-1}$, 60–100% of baseline VO_{2peak}) for 12 weeks. Contrary to prior reports and our preclinical data, there were no significant changes in any echocardiographic measures in either group from baseline to 12 weeks, although the AC-induced increase in ANP was attenuated by exercise training.[67]

Exercise and Treatment of DOX-Induced Cardiotoxicity

Two studies investigated the efficacy of aerobic exercise to treat / mitigate established cardiac injury caused by DOX exposure. Specifically, Combs et al.[59] hypothesized that an acute bout of aerobic exercise following DOX treatment would exacerbate drug-induced cardiotoxicity as evidenced by a decrease in survival rate. Results indicated that the survival rate was actually increased in exercised mice. Heon and colleagues[63] also demonstrated that cardiac proapoptotic markers were decreased in rats exercised for 2 weeks after DOX exposure. However, as cardiac assessments were not performed in these studies, it is not possible to determine whether exercise-induced improvements in cardiac function mediated the improvements in survival.

Potential Molecular Mechanisms Mediating Exercise-Induced Protection of DOX Injury

Several putative gene pathways have been postulated to mediate the protective properties of the exercise – DOX injury relationship (Table 4; Figure 2). These pathways are briefly described herein.

Exercise, ROS Damage, and Heat Shock Proteins

The central role of DOX-induced ROS in activation of the major pathways leading to cardiac injury suggests that exploitation of ROS generation and/or activity holds considerable therapeutic promise (Figure 1). Aerobic training protects the heart against ROS by enhancing endogenous antioxidant protective machinery (for an extensive review on the topic see Ascensao et al.).[72] Exercise has also been shown to mitigate DOX-induced ROS release (measured via cardiac tissue hydrogen peroxide as an indicator of superoxide production). Indeed, moderate intensity treadmill running prior to DOX not only blunts ROS production from cardiac mitochondria in murine models, but also significantly increases expression of antioxidant enzymes such as glutathione peroxidase 1, catalase, and manganese superoxide dismutase in cardiac tissue.[68] Exercise-induced increase in heat shock protein (HSP) 60 and 72 may also contribute, at least partially, to myocardial protection from DOX. The putative mechanisms by which HSP can protect cardiomyocytes include control of protein folding, prevention of denaturation and aggregation of intracellular proteins, and acceleration of the breakdown of damaged proteins.[73]

Exercise and Myofilament Apoptosis

Aerobic training may be cardioprotective by regulating proapoptotic signaling. Ascensao et al.[57] and Chicco and colleagues[62] report exercise prevents DOX-induced increases in the activities of the proapoptotic mediators Bax and tissue caspase-3. In an elegant study, Werner et al.[70] demonstrated that short-term running (21 days) reduced cardiac expression of p53 (an apoptotic mediator) by one-half in DOX treated mice, and potently decreased apoptotic cardiomyocytes by 5-fold.

Exercise and Suppression of Myofilament Protein Synthesis

Aerobic training may stimulate mobilization and homing of CPCs, and consequently limit myocyte turn-over following DOX. This notion has not been examined in cancer models, however Kolwicz et al.[74] found that exercise attenuated cardiomyocyte apoptosis, increased CPC proliferation by ~200% and augmented the presence of KIT positive cells (a stem cell factor crucial for the mobilization of progenitor cells to sites of injury) in the heart.[75] Together, this led to a higher abundance of cardiomyocytes in exercised relative to sedentary animals. Thus, aerobic exercise could increase the release, mobilization, and homing of CPCs following DOX insult to facilitate the reparative response.[75] Identification of the nuclear effectors of exercise may provide insight into the regulatory pathways of CPC release and myocyte survival. Intriguingly, genetic or pharmacologic enhancement of GATA-4 prevents cardiomyocyte apoptosis and drug-induced cardiotoxicity.[76] Bostrom and colleagues[47] demonstrated that aerobic exercise significantly increases GATA-4 mRNA, suggesting that exercise regulation of this factor is plausible given that GATA-4 levels are regulated by alpha 1-adrenergic agonists, which are modulated by exercise.[77]

Exercise and Ultrastructural Changes to Myocytes

Aerobic exercise elicits favorable adaptations in myocardial calcium handling, which could limit cardiotoxicity by preventing calcium overload in the myocyte. Indeed, exercise reverses systolic and diastolic dysfunction by improving calcium handling (SR calcium

release, diastolic SR calcium leak, and SR calcium sequestration).[52, 78, 79] Modulation of calpain activation may also be implicated. French et al.[80] found that acute aerobic exercise attenuated ischemic/reperfusion-induced calpain activation in rats. Importantly, these events were associated with protection against ischemia and cardiomyocyte apoptosis after an ischemia/reperfusion insult; it is not known if such events translate to the setting of DOX-induced injury.

Exercise and Alterations in Cardiac Energy Metabolism

AMPK is activated in response to changes in cellular energy, primarily a rise in AMP and a decrease in ATP or PCr. Exercise is a potent activator of AMPK activity in skeletal muscle via phosphorylation of ACC and a consequent decrease in malonyl-CoA leading to acute stimulation of fatty acid oxidation.[81, 82] Aerobic training is also a potent modulator of AMPK activity in cardiac tissue. Coven et al.[83] demonstrated that acute exercise increased total AMPK activity as well as both α-isoforms of the catalytic subunit of AMPK and all AMPK downstream targets (e.g., ACC phosphorylation). It therefore appears biologically plausible that aerobic exercise, as a potent activator of cardiac AMPK, may protect cardiac cells against DOX-induced toxicity, although no study to date has investigated this.

Future Directions: The Role of Aerobic Exercise to Modulate Cardiotoxicity

Timing, Intensity and Volume of Aerobic Exercise

More cardiotoxicity studies are required during and after DOX therapy both in clinically relevant murine models and in human trials. Two-thirds of the literature examined the impact of exercise prior to DOX exposure. Because the timeline between cancer diagnosis and initiation of anthracycline chemotherapy is generally very short, the translational relevance of these findings is limited; therefore particular attention should be given to exercise and treatment of DOX-induced cardiotoxicity. Investigation of the effects of different exercise intensities and volumes for the modulation of DOX injury is also required. Currently, the most appropriate and efficacious exercise prescription for preventing and/or treating anthracycline-induced cardiotoxicity is not known. In addition to mechanistically-driven investigations, human studies are required to compare the effects of different aerobic exercise prescriptions on cardiac function following an acute bout of aerobic exercise, during, and following DOX therapy. One intriguing area is the oxidative, metabolic, and functional cardiac consequences of high intensity aerobic exercise. These translational approaches will lead to better understanding of the role of aerobic exercise in preventing and/or treating cardiotoxicity.

Molecular Mechanisms of Aerobic Exercise Cardioprotection

Elucidation of the potential molecular mechanisms by which aerobic exercise reduces DOX-induced intrinsic cardiac dysfunction and improves inotropy and lusitropy is needed. For instance, the relationship between exercise, proapoptotic mediators and cardiac function in preclinical and clinical models would establish if aerobic exercise can prevent DOX-induced death of myocytes. Work is also needed to characterize not only the contribution of exercise-induced generation of CPCs in improving repair of damaged myocardium and limiting cardiotoxicity, but also the underlying molecular mechanisms resulting in upregulation of cardiomyocyte proliferation (e.g. GATA-4). Given the DOX-induced downregulation of AMPK, future investigations should consider the effects of exercise on AMPK activation and its downstream targets on cardiac function. Furthermore, based on experimental work in rat[84] and human skeletal muscle,[85] exercise-induced neuregulin signaling could be cardioprotective.[86] Increasing activity of neuregulin has importantly been shown to promote myocardial regeneration after injury,[87] and improve survival and cardiac function following DOX-induced HF.[88] Confirmation of these underlying mechanisms could be established via

exploitation of novel animal models such as transgenic models and other techniques such as organ-targeted ribonucleic acid interference (RNAi), which may be of use to identify exercise-induced gene functions.

Novel Markers of Cardiotoxicity

Sensitive cardiac imaging techniques need to be integrated into future studies. Specifically, newer techniques which combine detailed quantification of myocardial function (e.g. strain, twisting, and untwisting),[89, 90] and metabolic (e.g. ATP/PCr) evaluation of the heart using cardiac magnetic resonance imaging holds promise for early detection of changes in cardiac performance as a result of exercise and/or cancer therapy. The use of plasma (circulating) biomarkers, in conjunction with imaging modalities, might identify signatures associated with injury phenotypes and may also be helpful in identifying those patients who would benefit most from exercise training.

Looking Past the Heart

Cardiac function is one component of a highly integrated system responsible for the transport of O_2 (lung-cardiac-vascular-muscle function axis) for ATP resynthesis in the skeletal muscle. As such, when evaluating cardiac injury, it is also important to consider injury to other O_2 transport organs. Exercise is one of a limited number of interventions that can augment the reserve capacity of several O_2 transport organs, and therefore stands to have tremendous clinical benefits for patients receiving DOX for solid malignancies. Indeed, we recently found that DOX-containing chemotherapy caused a significant decline in VO_{2peak} despite normal LV function in women with breast cancer.[67] In contrast, supervised aerobic exercise training caused significant improvements in VO_{2peak} during concurrent DOX therapy, despite decreased hemoglobin and negligible changes in LV function.

Other Patient Populations

The modulation of DOX-induced cardiotoxicity by aerobic exercise in other patient groups should be investigated. In particular, cardiovascular disease is a major cause of morbidity and possibly premature mortality in adult survivors of childhood cancers.[91, 92] It is possible that normal physiological hypertrophy is significantly blunted in children undergoing chemotherapy via mechanisms discussed in previous sections. Given that exercise activates physiological hypertrophy of the heart,[46] aerobic training in pediatric cancer patients could act as a crucial modulator of anthracycline-induced cardiotoxicity, thus preventing late occurring cardiac effects.

Conclusions

Cardiotoxicity is a frequent and devastating adverse complication of DOX therapy leading to morbidity, poor quality of life, and premature mortality. Evidence reviewed here indicates that aerobic exercise is a promising strategy to prevent and/or treat DOX-induced cardiac injury. Future studies are required to further elucidate the molecular mechanisms underlying the cardioprotective properties of exercise before, during and after DOX exposure. Collectively, hypothesis-driven translational studies are required to define the nature and magnitude of the cardioprotective effects of exercise in the setting of anthracycline chemotherapy. Such research will lead to mechanistically-driven clinical trials which, in turn, will inform exercise prescription rehabilitation guidelines for breast cancer and patients with other solid anthracycline-sensitive malignancies.

Acknowledgments

Funding Sources

This work was supported in part by Natural Sciences and Engineering Research Council Post Doctoral Fellowship (JMS); NIH CA143254, CA142566, CA138634, CA133895, CA125458, funds from George and Susan Beischer (LWJ).

References

1. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, Muggia FM. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979; 91:710–717. [PubMed: 496103]
2. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003; 97:2869–2879. [PubMed: 12767102]
3. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol. 2007; 50:1435–1441. [PubMed: 17919562]
4. Eisele JC, Schaefer IM, Randel Nyengaard J, Post H, Liebetanz D, Bruel A, Muhlfeld C. Effect of voluntary exercise on number and volume of cardiomyocytes and their mitochondria in the mouse left ventricle. Basic Res Cardiol. 2008; 103:12–21. [PubMed: 18004633]
5. Kavazis AN, McClung JM, Hood DA, Powers SK. Exercise induces a cardiac mitochondrial phenotype that resists apoptotic stimuli. Am J Physiol Heart Circ Physiol. 2008; 294:H928–H935. [PubMed: 18083894]
6. Laurent G, Jaffrezou JP. Signaling pathways activated by daunorubicin. Blood. 2001; 98:913–924. [PubMed: 11493433]
7. Perego P, Corna E, De Cesare M, Gatti L, Polizzi D, Pratesi G, Supino R, Zunino F. Role of apoptosis and apoptosis-related genes in cellular response and antitumor efficacy of anthracyclines. Curr Med Chem. 2001; 8:31–37. [PubMed: 11172690]
8. Gewirtz DA. A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics adriamycin and daunorubicin. Biochem Pharmacol. 1999; 57:727–741. [PubMed: 10075079]
9. Doroshow JH. Effect of anthracycline antibiotics on oxygen radical formation in rat heart. Cancer Res. 1983; 43:460–472. [PubMed: 6293697]
10. Doroshow JH, Locker GY, Ifrim I, Myers CE. Prevention of doxorubicin cardiac toxicity in the mouse by N-acetylcysteine. J Clin Invest. 1981; 68:1053–1064. [PubMed: 7287901]
11. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev. 2004; 56:185–229. [PubMed: 15169927]
12. Lim CC, Zuppinger C, Guo X, Kuster GM, Helmes M, Eppenberger HM, Suter TM, Liao R, Sawyer DB. Anthracyclines induce calpain-dependent titin proteolysis and necrosis in cardiomyocytes. J Biol Chem. 2004; 279:8290–8299. [PubMed: 14676206]
13. Olson RD, Mushlin PS. Doxorubicin cardiotoxicity: analysis of prevailing hypotheses. FASEB J. 1990; 4:3076–3086. [PubMed: 2210154]
14. Minotti G, Mancuso C, Frustaci A, Mordente A, Santini SA, Calafiore AM, Liberi G, Gentiloni N. Paradoxical inhibition of cardiac lipid peroxidation in cancer patients treated with doxorubicin. Pharmacologic and molecular reappraisal of anthracycline cardiotoxicity. J Clin Invest. 1996; 98:650–661. [PubMed: 8698856]
15. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. N Engl J Med. 1998; 339:900–905. [PubMed: 9744975]
16. Sano M, Minamino T, Toko H, Miyauchi H, Orimo M, Qin Y, Akazawa H, Tateno K, Kayama Y, Harada M, Shimizu I, Asahara T, Hamada H, Tomita S, Molkentin JD, Zou Y, Komuro I. p53-induced inhibition of Hif-1 causes cardiac dysfunction during pressure overload. Nature. 2007; 446:444–448. [PubMed: 17334357]
17. Zhu W, Zou Y, Aikawa R, Harada K, Kudoh S, Uozumi H, Hayashi D, Gu Y, Yamazaki T, Nagai R, Yazaki Y, Komuro I. MAPK superfamily plays an important role in daunomycin-induced apoptosis of cardiac myocytes. Circulation. 1999; 100:2100–2107. [PubMed: 10562267]
18. Yamamoto Y, Hoshino Y, Ito T, Nariai T, Mohri T, Obana M, Hayata N, Uozumi Y, Maeda M, Fujio Y, Azuma J. Atrogin-1 ubiquitin ligase is upregulated by doxorubicin via p38-MAP kinase in cardiac myocytes. Cardiovasc Res. 2008; 79:89–96. [PubMed: 18346979]

19. Shizukuda Y, Matoba S, Mian OY, Nguyen T, Hwang PM. Targeted disruption of p53 attenuates doxorubicin-induced cardiac toxicity in mice. Mol Cell Biochem. 2005; 273:25–32. [PubMed: 16013437]
20. Kang YJ, Zhou ZX, Wang GW, Buridi A, Klein JB. Suppression by metallothionein of doxorubicin-induced cardiomyocyte apoptosis through inhibition of p38 mitogen-activated protein kinases. J Biol Chem. 2000; 275:13690–13698. [PubMed: 10788488]
21. Lewinter MM, Vanburen P. Myofilament remodeling during the progression of heart failure. J Card Fail. 2002; 8:S271–S275. [PubMed: 12555132]
22. De Angelis A, Piegari E, Cappetta D, Marino L, Filippelli A, Berrino L, Ferreira-Martins J, Zheng H, Hosoda T, Rota M, Urbanek K, Kajstura J, Leri A, Rossi F, Anversa P. Anthracycline cardiomyopathy is mediated by depletion of the cardiac stem cell pool and is rescued by restoration of progenitor cell function. Circulation. 121:276–292. [PubMed: 20038740]
23. Charron F, Nemer M. GATA transcription factors and cardiac development. Semin Cell Dev Biol. 1999; 10:85–91. [PubMed: 10355032]
24. Kim Y, Ma AG, Kitta K, Fitch SN, Ikeda T, Ihara Y, Simon AR, Evans T, Suzuki YJ. Anthracycline-induced suppression of GATA-4 transcription factor: implication in the regulation of cardiac myocyte apoptosis. Mol Pharmacol. 2003; 63:368–377. [PubMed: 12527808]
25. Kemi OJ, Ellingsen O, Smith GL, Wisloff U. Exercise-induced changes in calcium handling in left ventricular cardiomyocytes. Front Biosci. 2008; 13:356–368. [PubMed: 17981553]
26. Keung EC, Toll L, Ellis M, Jensen RA. L-type cardiac calcium channels in doxorubicin cardiomyopathy in rats morphological, biochemical, and functional correlations. J Clin Invest. 1991; 87:2108–2113. [PubMed: 1645752]
27. Saeki K, Obi I, Ogiku N, Shigekawa M, Imagawa T, Matsumoto T. Doxorubicin directly binds to the cardiac-type ryanodine receptor. Life Sci. 2002; 70:2377–2389. [PubMed: 12150202]
28. Logue SE, Gustafsson AB, Samali A, Gottlieb RA. Ischemia/reperfusion injury at the intersection with cell death. J Mol Cell Cardiol. 2005; 38:21–33. [PubMed: 15623419]
29. Chen M, Won DJ, Krajewski S, Gottlieb RA. Calpain and mitochondria in ischemia/reperfusion injury. J Biol Chem. 2002; 277:29181–29186. [PubMed: 12042324]
30. Gustafsson AB, Gottlieb RA. Mechanisms of apoptosis in the heart. J Clin Immunol. 2003; 23:447–459. [PubMed: 15031632]
31. Conway MA, Allis J, Ouwerkerk R, Niioka T, Rajagopalan B, Radda GK. Detection of low phosphocreatine to ATP ratio in failing hypertrophied human myocardium by 31P magnetic resonance spectroscopy. Lancet. 1991; 338:973–976. [PubMed: 1681342]
32. Conway MA, Bristow JD, Blackledge MJ, Rajagopalan B, Radda GK. Cardiac metabolism during exercise in healthy volunteers measured by 31P magnetic resonance spectroscopy. Br Heart J. 1991; 65:25–30. [PubMed: 1993127]
33. Ingwall JS, Weiss RG. Is the failing heart energy starved? On using chemical energy to support cardiac function. Circ Res. 2004; 95:135–145. [PubMed: 15271865]
34. Seraydarian MW, Artaza L, Goodman MF. Adriamycin: effect on mammalian cardiac cells in culture. I. Cell population and energy metabolism. J Mol Cell Cardiol. 1977; 9:375–382. [PubMed: 559773]
35. Pattynama PM, Lamb HJ, van der Velde EA, van der Wall EE, de Roos A. Left ventricular measurements with cine and spin-echo MR imaging: a study of reproducibility with variance component analysis. Radiology. 1993; 187:261–268. [PubMed: 8451425]
36. Hartiala JJ, Mostbeck GH, Foster E, Fujita N, Dulce MC, Chazouilleres AF, Higgins CB. Velocity-encoded cine MRI in the evaluation of left ventricular diastolic function: measurement of mitral valve and pulmonary vein flow velocities and flow volume across the mitral valve. Am Heart J. 1993; 125:1054–1066. [PubMed: 8465728]
37. Neumann D, Schlattner U, Wallimann T. A molecular approach to the concerted action of kinases involved in energy homoeostasis. Biochem Soc Trans. 2003; 31:169–174. [PubMed: 12546678]
38. Tokarska-Schlattner M, Zaugg M, da Silva R, Lucchinetti E, Schaub MC, Wallimann T, Schlattner U. Acute toxicity of doxorubicin on isolated perfused heart: response of kinases regulating energy supply. Am J Physiol Heart Circ Physiol. 2005; 289:H37–H47. [PubMed: 15764680]

39. Lee K, Qian DZ, Rey S, Wei H, Liu JO, Semenza GL. Anthracycline chemotherapy inhibits HIF-1 transcriptional activity and tumor-induced mobilization of circulating angiogenic cells. Proc Natl Acad Sci U S A. 2009; 106:2353–2358. [PubMed: 19168635]
40. Fujimoto N, Prasad A, Hastings JL, Arbab-Zadeh A, Bhella PS, Shibata S, Palmer D, Levine BD. Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. Circulation. 122:1797–1805. [PubMed: 20956204]
41. Ventura-Clapier R, Mettauer B, Bigard X. Beneficial effects of endurance training on cardiac and skeletal muscle energy metabolism in heart failure. Cardiovasc Res. 2007; 73:10–18. [PubMed: 17045979]
42. Hambrecht R, Fiehn E, Weigl C, Gielen S, Hamann C, Kaiser R, Yu J, Adams V, Niebauer J, Schuler G. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation. 1998; 98:2709–2715. [PubMed: 9851957]
43. Mezzani A, Corra U, Giannuzzi P. Central adaptations to exercise training in patients with chronic heart failure. Heart Fail Rev. 2008; 13:13–20. [PubMed: 17932747]
44. Jessup M, Brozena S. Heart failure. N Engl J Med. 2003; 348:2007–2018. [PubMed: 12748317]
45. Kehat I, Molkentin JD. Molecular pathways underlying cardiac remodeling during pathophysiological stimulation. Circulation. 122:2727–2735. [PubMed: 21173361]
46. McMullen JR, Amirahmadi F, Woodcock EA, Schinke-Braun M, Bouwman RD, Hewitt KA, Mollica JP, Zhang L, Zhang Y, Shioi T, Buerger A, Izumo S, Jay PY, Jennings GL. Protective effects of exercise and phosphoinositide 3-kinase(p110alpha) signaling in dilated and hypertrophic cardiomyopathy. Proc Natl Acad Sci U S A. 2007; 104:612–617. [PubMed: 17202264]
47. Bostrom P, Mann N, Wu J, Quintero PA, Plovie ER, Panakova D, Gupta RK, Xiao C, Macrae CA, Rosenzweig A, Spiegelman BM. C/EBPbeta Controls Exercise-Induced Cardiac Growth and Protects against Pathological Cardiac Remodeling. Cell. 143:1072–1083. [PubMed: 21183071]
48. Flynn KE, Pina IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009; 301:1451–1459. [PubMed: 19351942]
49. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Pina IL. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009; 301:1439–1450. [PubMed: 19351941]
50. Jones LW, Liang Y, Pituskin EN, Battaglini CL, Scott JM, Hornsby WE, Haykowsky M. Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. Oncologist. 16:112–120. [PubMed: 21212429]
51. Wisloff U, Loennechen JP, Falck G, Beisvag V, Currie S, Smith G, Ellingsen O. Increased contractility and calcium sensitivity in cardiac myocytes isolated from endurance trained rats. Cardiovasc Res. 2001; 50:495–508. [PubMed: 11376625]
52. Wisloff U, Loennechen JP, Currie S, Smith GL, Ellingsen O. Aerobic exercise reduces cardiomyocyte hypertrophy and increases contractility, Ca2+ sensitivity and SERCA-2 in rat after myocardial infarction. Cardiovasc Res. 2002; 54:162–174. [PubMed: 12062372]
53. Kemi OJ, Haram PM, Loennechen JP, Osnes JB, Skomedal T, Wisloff U, Ellingsen O. Moderate vs. high exercise intensity: differential effects on aerobic fitness, cardiomyocyte contractility, and endothelial function. Cardiovasc Res. 2005; 67:161–172. [PubMed: 15949480]
54. Diffee GM, Chung E. Altered single cell force-velocity and power properties in exercise-trained rat myocardium. J Appl Physiol. 2003; 94:1941–1948. [PubMed: 12524379]
55. Natali AJ, Wilson LA, Peckham M, Turner DL, Harrison SM, White E. Different regional effects of voluntary exercise on the mechanical and electrical properties of rat ventricular myocytes. J Physiol. 2002; 541:863–875. [PubMed: 12068046]
56. Ascensao A, Lumini-Oliveira J, Machado NG, Ferreira RM, Goncalves IO, Moreira AC, Marques F, Sardao VA, Oliveira PJ, Magalhaes J. Acute exercise protects against calcium-induced cardiac

mitochondrial permeability transition pore opening in doxorubicin-treated rats. Clin Sci (Lond). 120:37–49. [PubMed: 20666733]

57. Ascensao A, Magalhaes J, Soares JM, Ferreira R, Neuparth MJ, Marques F, Oliveira PJ, Duarte JA. Moderate endurance training prevents doxorubicin-induced in vivo mitochondriopathy and reduces the development of cardiac apoptosis. Am J Physiol Heart Circ Physiol. 2005; 289:H722–H731. [PubMed: 15792986]
58. Ascensao A, Magalhaes J, Soares J, Ferreira R, Neuparth M, Marques F, Oliveira J, Duarte J. Endurance training attenuates doxorubicin-induced cardiac oxidative damage in mice. Int J Cardiol. 2005; 100:451–460. [PubMed: 15837090]
59. Combs AB, Hudman SL, Bonner HW. Effect of exercise stress upon the acute toxicity of adriamycin in mice. Res Commun Chem Pathol Pharmacol. 1979; 23:395–398. [PubMed: 461964]
60. Chicco AJ, Hydock DS, Schneider CM, Hayward R. Low-intensity exercise training during doxorubicin treatment protects against cardiotoxicity. J Appl Physiol. 2006; 100:519–527. [PubMed: 16210442]
61. Chicco AJ, Schneider CM, Hayward R. Voluntary exercise protects against acute doxorubicin cardiotoxicity in the isolated perfused rat heart. Am J Physiol Regul Integr Comp Physiol. 2005; 289:R424–R431. [PubMed: 15845878]
62. Chicco AJ, Schneider CM, Hayward R. Exercise training attenuates acute doxorubicin-induced cardiac dysfunction. J Cardiovasc Pharmacol. 2006; 47:182–189. [PubMed: 16495754]
63. Heon S, Bernier M, Servant N, Dostanic S, Wang C, Kirby GM, Alpert L, Chalifour LE. Dexrazoxane does not protect against doxorubicin-induced damage in young rats. Am J Physiol Heart Circ Physiol. 2003; 285:H499–H506. [PubMed: 12714334]
64. Hydock DS, Wonders KY, Schneider CM, Hayward R. Voluntary wheel running in rats receiving doxorubicin: effects on running activity and cardiac myosin heavy chain. Anticancer Res. 2009; 29:4401–4407. [PubMed: 20032385]
65. Hydock DS, Lien CY, Schneider CM, Hayward R. Effects of voluntary wheel running on cardiac function and myosin heavy chain in chemically gonadectomized rats. Am J Physiol Heart Circ Physiol. 2007; 293:H3254–H3264. [PubMed: 17906105]
66. Ji LL, Mitchell EW. Effects of Adriamycin on heart mitochondrial function in rested and exercised rats. Biochem Pharmacol. 1994; 47:877–885. [PubMed: 8135863]
67. Jones, L.; Dolinsky, VW.; Haykowsky, MJ.; Patterson, I.; Douglas, PS.; Allen, JD.; Scott, JM.; Rogan, K.; Khouri, M.; West, M.; Hornsby, WE.; Young, ME.; Peppercorn, J.; Marcom, K.; Blackwell, KL.; Kimmick, G.; Dyck, JR. Effects of aerobic training to improve cardiovascular function and prevent cardiac remodeling after cytotoxic therapy in early breast cancer; Poster to be presented at the 102nd American Association of Cancer Research Annual Meeting; Orlando FL, USA: 2011 April.
68. Kavazis AN, Smuder AJ, Min K, Tumer N, Powers SK. Short-term exercise training protects against doxorubicin induced cardiac mitochondrial damage independent of HSP72. Am J Physiol Heart Circ Physiol.
69. Kanter MM, Hamlin RL, Unverferth DV, Davis HW, Merola AJ. Effect of exercise training on antioxidant enzymes and cardiotoxicity of doxorubicin. J Appl Physiol. 1985; 59:1298–1303. [PubMed: 4055607]
70. Werner C, Hanhoun M, Widmann T, Kazakov A, Semenov A, Poss J, Bauersachs J, Thum T, Pfreundschuh M, Muller P, Haendeler J, Bohm M, Laufs U. Effects of physical exercise on myocardial telomere-regulating proteins, survival pathways, and apoptosis. J Am Coll Cardiol. 2008; 52:470–482. [PubMed: 18672169]
71. Wonders KY, Hydock DS, Schneider CM, Hayward R. Acute exercise protects against doxorubicin cardiotoxicity. Integr Cancer Ther. 2008; 7:147–154. [PubMed: 18815146]
72. Ascensao A, Ferreira R, Magalhaes J. Exercise-induced cardioprotection--biochemical, morphological and functional evidence in whole tissue and isolated mitochondria. Int J Cardiol. 2007; 117:16–30. [PubMed: 16860886]
73. Powers SK, Locke, Demirel HA. Exercise, heat shock proteins, and myocardial protection from I-R injury. Med Sci Sports Exerc. 2001; 33:386–392. [PubMed: 11252064]

74. Kolwicz SC, MacDonnell SM, Kendrick ZV, Houser SR, Libonati JR. Voluntary wheel running and pacing-induced dysfunction in hypertension. Clin Exp Hypertens. 2008; 30:565–573. [PubMed: 18855260]
75. Force T, Kerkela R. Cardiotoxicity of the new cancer therapeutics--mechanisms of, and approaches to, the problem. Drug Discov Today. 2008; 13:778–784. [PubMed: 18617014]
76. Aries A, Paradis P, Lefebvre C, Schwartz RJ, Nemer M. Essential role of GATA-4 in cell survival and drug-induced cardiotoxicity. Proc Natl Acad Sci U S A. 2004; 101:6975–6980. [PubMed: 15100413]
77. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. J Am Coll Cardiol. 2009; 54:1747–1762. [PubMed: 19874988]
78. Kemi OJ, Ceci M, Condorelli G, Smith GL, Wisloff U. Myocardial sarcoplasmic reticulum Ca2+ ATPase function is increased by aerobic interval training. Eur J Cardiovasc Prev Rehabil. 2008; 15:145–148. [PubMed: 18391639]
79. Kemi OJ, Wisloff U. High-intensity aerobic exercise training improves the heart in health and disease. J Cardiopulm Rehabil Prev. 30:2–11. [PubMed: 20040880]
80. French JP, Hamilton KL, Quindry JC, Lee Y, Upchurch PA, Powers SK. Exercise-induced protection against myocardial apoptosis and necrosis: MnSOD, calcium-handling proteins, and calpain. FASEB J. 2008; 22:2862–2871. [PubMed: 18417547]
81. Rasmussen BB, Hancock CR, Winder WW. Postexercise recovery of skeletal muscle malonyl-CoA, acetyl-CoA carboxylase, and AMP-activated protein kinase. J Appl Physiol. 1998; 85:1629–1634. [PubMed: 9804562]
82. Rasmussen BB, Winder WW. Effect of exercise intensity on skeletal muscle malonyl-CoA and acetyl-CoA carboxylase. J Appl Physiol. 1997; 83:1104–1109. [PubMed: 9338417]
83. Coven DL, Hu X, Cong L, Bergeron R, Shulman GI, Hardie DG, Young LH. Physiological role of AMP-activated protein kinase in the heart: graded activation during exercise. Am J Physiol Endocrinol Metab. 2003; 285:E629–E636. [PubMed: 12759223]
84. Lebrasseur NK, Cote GM, Miller TA, Fielding RA, Sawyer DB. Regulation of neuregulin/ErbB signaling by contractile activity in skeletal muscle. Am J Physiol Cell Physiol. 2003; 284:C1149–C1155. [PubMed: 12519750]
85. LeBrasseur NK, Mizer KC, Parkington JD, Sawyer DB, Fielding RA. The expression of neuregulin and erbB receptors in human skeletal muscle: effects of progressive resistance training. Eur J Appl Physiol. 2005; 94:371–375. [PubMed: 15875210]
86. Peng X, Chen B, Lim CC, Sawyer DB. The cardiotoxicology of anthracycline chemotherapeutics: translating molecular mechanism into preventative medicine. Mol Interv. 2005; 5:163–171. [PubMed: 15994456]
87. Bersell K, Arab S, Haring B, Kuhn B. Neuregulin1/ErbB4 signaling induces cardiomyocyte proliferation and repair of heart injury. Cell. 2009; 138:257–270. [PubMed: 19632177]
88. Bian Y, Sun M, Silver M, Ho KK, Marchionni MA, Caggiano AO, Stone JR, Amende I, Hampton TG, Morgan JP, Yan X. Neuregulin-1 attenuated doxorubicin-induced decrease in cardiac troponins. Am J Physiol Heart Circ Physiol. 2009; 297:H1974–H1983. [PubMed: 19801490]
89. Esch BT, Scott JM, Warburton DE, Thompson R, Taylor D, Baron JC, Paterson I, Haykowsky MJ. Left ventricular torsion and untwisting during exercise in heart transplant recipients. J Physiol. 2009; 587:2375–2386. [PubMed: 19332498]
90. Scott JM, Esch BT, Haykowsky MJ, Paterson I, Warburton DE, Chow K, Cheng Baron J, Lopaschuk GD, Thompson RB. Effects of high intensity exercise on biventricular function assessed by cardiac magnetic resonance imaging in endurance trained and normally active individuals. Am J Cardiol. 106:278–283. [PubMed: 20599016]
91. Franco VI, Henkel JM, Miller TL, Lipshultz SE. Cardiovascular effects in childhood cancer survivors treated with anthracyclines. Cardiol Res Pract. 2011:134679. [PubMed: 21331374]
92. Chen MH, Colan SD, Diller L. Cardiovascular disease: cause of morbidity and mortality in adult survivors of childhood cancers. Circ Res. 108:619–628. [PubMed: 21372293]

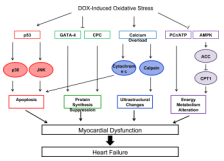

Figure 1.

Mechanisms underlying DOX-induced cardiotoxicity. DOX-induced generation of ROS is a central mediator of: 1) accelerated myofilament apoptosis via upregulation of p53-MAPK pathway, 2) suppression of myofilament protein synthesis via inhibition of CPCs and GATA-4, 3) alterations in cardiac energy metabolism via downregulation of PCr/ATP and AMPK, 4) ultrastructural changes to myocytes via upregulation of calpain and cytochrome c. These changes lead to left ventricular pathological hypertrophy and ultimately heart failure. DOX, doxorubicin; ROS, reactive oxygen species; mitogen activated protein kinases, MAPK; cardiac progenitor cells, CPCs; phosphocreatine, PCr; adenosine triphosphate, ATP; AMP-activated protein kinase, AMPK.

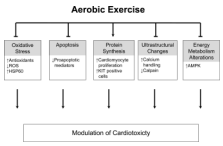

Figure 2.

Mechanisms underlying modulation of DOX-induced cardiotoxicity through aerobic exercise. Hsp, heat shock protein; ROS, reactive oxygen species; AMP-activated protein kinase, AMPK.

Table 1

Stages of doxorubicin-induced cardiotoxicity.

Cardiotoxicity Stage	Time	Symptoms
Acute	Within 1 week of therapy	Supraventricular and ventricular arrhythmias, acute coronary syndromes, acute pericarditis/myocarditis
Early	Within 1 year of therapy	Progressive LV dilation, LV wall thinning, decreased contractility
Late	After 1 year of therapy	LV dysfunction, arrhythmias, HF

Abbreviations: LV, left ventricle; HF, heart failure.

Table 2

Effects of aerobic exercise on cardiac function in healthy individuals and systolic heart failure (HF) patients.

Parameter	Healthy	Systolic HF
Resting		
LV end-diastolic volume	↑	↓
LV end-systolic volume	↔	↓
LV ejection fraction	↔	↑
LV stroke volume	↑	↓
LV mass	↑	↓
Maximal Exercise		
Maximal oxygen uptake	↑	↑
LV end-diastolic volume	↑	↓
LV end-systolic volume	↔	↓
LV ejection fraction	↔	↑
LV stroke volume	↑	↑

Abbreviations: LV, left ventricle; HF, heart failure.

Note: downward pointing arrow (↓) indicates a decrease; upward pointing arrow (↑) indicates an increase, ↔ indicates no change.

Table 3

Summary of studies investigating the effects of aerobic exercise on prevention and/or treatment of doxorubicin-induced cardiotoxicity

Author	Animal Species	DOX Schedule	Exercise	Outcome
Ascensao et al. (2011)[56]	Rats	Bolus (20 mg/kg)	Acute exercise (60 min) Pre-DOX	Maintained mitochondrial function in exercise group
Ascensao et al. (2005)[57]	Mice	Bolus (20 mg/kg)	60–90min/d; 5d/wk; 14 wks Pre-DOX	↓ ROS production, oxidative damage and apoptosis in ET group
Ascensao et al. (2005)[58]	Mice	Bolus (20 mg/kg)	60–90min/d; 5d/wk; 14 wks Pre-DOX	↑ glutathione, HSP60 in ET group
Combs et al. (1978)[59]	Mice	Bolus (23 mg/kg)	Acute exercise (30 min) Post-DOX	Improved survival in exercise group
Chicco et al. (2006)[60]	Rats	Bolus (15 mg/kg)	20min/d; 5 d/wk; 2 wks During DOX	Maintained dP/dt_{max}, dP/dt_{min} and coronary flow in ET group
Chicco et al. (2005)[61]	Rats	10 μM for 60 min (perfused hearts)	Voluntary exercise; 8 wks Pre-DOX	↑ HSP72, maintained dP/dt_{max}, dP/dt_{min} in ET group
Chicco et al. (2006)[62]	Rats	2.5 mg/kg; 3 days/wk for 2 wks	20–60min/d; 5d/wk; 12 wks Pre-DOX	↑ HSP72, maintained dP/dt_{max}, dP/dt_{min} in ET group
Heon et al. (2003)[63]	Rats	Bolus (3 mg/kg)	10–45min/d; 7d/wk; 2 wks Post-DOX	↓expression of proapoptotic markers
Hydock et al. (2009)[64]	Rats	2.5 mg/kg; 1 day/wk for 6 wks	Voluntary exercise; 6 wks During DOX	Maintained α-MHC isoform in ET group
Hydock et al. (2007)[65]	Rats	Bolus (10 mg/kg)	Voluntary exercise; 10 wks Pre-DOX	Attenuated ↑ β-MHC isoform, maintained dP/dt_{max}, dP/dt_{min} in ET group
Ji et al. (1994)[66]	Rats	Bolus (4 mg/kg; twice)	Acute exercise (60 min) Pre-DOX	Maintained mitochondrial respiration
Jones et al. (2011)[67]	Mice	8mg/kg; 1 day/wk for 4 wks	45 min/day; 5d/wk; 8 wks During DOX	↓ LV dysfunction, attenuated ↑ in SERCA2a and ANP in ET group
Jones et al. (2011)[67]	Humans	60 mg/m^2	60 min/day; 3d/wk; 12 wks During DOX	↑ aerobic capacity and attenuated ↑ in ANP in ET group
Kavazis et al. (2010)[68]	Rats	Bolus (20 mg/kg)	60 min/day; 5 consecutive days (estimated work rate of 70% VO_{2max}) Pre-DOX	↓ ROS production, oxidative damage, attenuated ↑ in calpain in ET group
Kanter et al. (1985)[69]	Rats	4 mg/kg; 2 days/wk for 7 wks	60min/d; 5d/wk; 21 wks During DOX	↓ histological damage in ET group
Werner et al. (2008)[70]	Rats	Bolus (22.5 mg/kg)	Voluntary exercise; 21 days Pre-DOX	↓ p53 expression in ET group
Wonders et al. (2008)[71]	Rats	Bolus (15 mg/kg)	Acute exercise (60 min) Pre-DOX	↑ LVESP, dP/dt_{max}, dP/dt_{min} in exercise group

Abbreviations: ROS, reactive oxygen species; ET, endurance trained; HSP, heat shock protein; dP/dt_{max}; maximal developed pressure velocity; dP/dt_{min}; minimal developed pressure velocity; MHC, myosin heavy chain; LVESP, left ventricular end systolic pressure; ANP, atrial naturietic peptide; SERCA 2a, cardiac sarcoplasmic reticulum calcium transporter.

Table 4

Mechanisms of doxorubicin-induced cardiotoxicity and anticipated modulatory effects of aerobic exercise.

Cellular and Molecular Changes	Pathway	Direction of Exercise Modulation
Apoptosis	Increased p53 expression Activation of p38 MAPK and JNK	↓ ↓
Suppression of Protein Synthesis	Depletion of CPCs Downregulation of GATA-4	↑ ↑
Ultrastructural Changes	Cytosolic calcium overload Cytochrome c release Activation of calpain	↓ ↓ ↓
Alterations in Energy Metabolism	Reduction in ATP and PCr Decrease in AMPK	↑ ↑

Abbreviations: mitogen activated protein kinases, MAPK; c-Jun N-terminal kinases, JNK; cardiac progenitor cells, CPCs; phosphocreatine, PCr; adenosine triphosphate, ATP; AMP-activated protein kinase, AMPK.

Note: downward pointing arrow (↓) indicates a decrease in effects; upward pointing arrow (↑) indicates an increase in effects.